Topical Nanoemulgel : A Novel Approach for Wound Healing Efficacy

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ABSTRACT

Tissue repair and wound healing are complex processes that involve inflammation, granulation, and remodelling of the tissue. The potential of various statins improve the wound healing effect was established. The nanoemulgel drug delivery system is a formulation related intervention to improve drug absorption and therapeutic profile of lipophilic drugs. Lipophilic drugs can be easily incorporated and the skin permeability of the incorporated drugs can be enhanced in several folds due to the finely distributed oil droplets in gel phase. Simultaneously, it can be targeted more specifically to the site of action and can avoid first pass metabolism and relieve the user from gastric/systemic incompatibilities. The nanoemulgel will shows better solubility and permeability of the active components at the site of application via opening of hair follicles or other routes, as compared to other formulations. This review will discuss the effect of topical nanoemulgel over other formulations for the wound healing efficacy.

Keywords: Nanoemulgel; Lipophilic drugs; Wound healing.

INTRODUCTION

Wound healing is a dynamic and complex biological process which requires orchestration of different cellular processes to help damaged skin restores its normal function and structure [1]. Thehealing process of the open wounds includes interdependent and overlapping stages of hemostasis, inflammation, proliferation, revascularization, and remodelling [2]. These phases must occur inan integrated sequence and in optimal intensity to properly allow wound healing [2]. Therefore, developing new treatment modalities for wound healing is highly required; especially as currentmedical therapies for wound care are limited. Statins are anti-hyperlipidemic agents that are widely used in patients to prevent cardiovascular events. Recently, statins have shown efficacy in the treatment of a wide variety of dermatologic disorders such as urticaria, psoriasis, and acne [2]. Because of their diverse pleiotropic effects, statins have been also suggested to be useful in wound healing as they can modulate cellular processes including inflammation, apoptosis, and proliferation. Besides, they are reported to decreaseoxidative stress and improve endothelial as well as microvascular functions which may have a rolein accelerating and enhancing healingprocesses. Indeed, various studies have evaluated the healing

efficacy of different statins, including simvastatin, atorvastatin (ATR), and pravastatin, onvarious skin wounds.

The most consistent results in wound healing came with ATRasecond-generation synthetic statinwhich was shown to have specific properties such as long half-life, active metabolites, lipophilicity, and high protein binding. Due to the multiple side effects of oral statins, including myopathy and liver toxicity topical drugdelivery system is suggested to be a reasonable alternative to oral statin in wound healing, as it providesbetter drug delivery with prolonged action and less side effects [3]. Transdermal drug delivery systems include transdermal patches, gels, and emulgels. Recently, nanoemulgel a novel approach for topical delivery of hydrophobic drugshas been reported to have several favourable propertiesincluding improved physical stability, non-toxicity, and a non-irritant nature. Apart from theseproperties, it exhibits a dual release control system hydrogel and nanoemulsion and has nano-sized particles which allow rapid permeation and delivery of active pharmaceutical ingredients. The previously mentioned characteristics of the nanoemulgel provide improved drug efficacy comparedto other traditional formulations in treatment of various skin diseases as well as bacterial and fungalinfections. The present study was conducted to develop different topical formulations of ATR using gel, emulgel, and nanoemulgel systems. Additionally, the study aimed to evaluate the woundhealing efficacy of ATR nanoemulgel compared to other gel formulations on excision wound-induced rats [3].

Emulgel

Emulgel is a combination of gel and emulsion where emulsion used can be both type W/O and O/W as a vehicle for purpose to deliver selected drug to the skin. Water Phase containing the gelling agent converts a classic emulsion in emulgel. Dermatological use of Emulgel has many favourable properties like easy spreadable, greaseless, being thixotropic, water-soluble, easy removal, longer shelf life, non-staining, and bio-friendly

Nanoemulgel

Formation containing Nanoemulsion in gel base are called nanoemulgel, is the addition of Nanoemulsion system intergraded into gel matrix which influences a better skin permeation. This mixture of nanomulgel acts as drug reservoirs, influencing the release of drug from inner phase to outer phase and further. Nanoemulgel on intact with skin release the oil droplets from the gel and this oil droplets penetrate into the SC of the skin and deliver the drug to intended site. Nanoemulsion-gel have a good adhesion property and high solubilising of drug in oil phase leads to larger concentration gradient towards the skin that further increase skin penetration of drug. Also patient compliance is improved due to increased spared ability compare to creams and ointments and decreased stickiness.

Advantage of Nanoemulgel

- Stability of Nanoemulsion is enhanced due to distribution of oil droplets in Gel base; where affinity of the drug toward oil determines stability.

- Also good adhesion on the skin with high solubilising power leads to high concentration gradient that increase penetration of drug as it moves down.

- Moreover, these types of formulation give support to delivery of lipophilic and poorly water soluble drugs and also improve patient compliance.

- Nanoemulgel also helps in controlled release of drugs having the shorter half-life.

- Provide higher Spread-ability of the formulation than creams.

- Nanoemulgel are Non-toxic and non irritant.

- Better loading of drug compare to other formulation.

- Increase skin permeability and drug deposition.

Rational

Topical dosage forms like cream, lotion, ointment have many disadvantages. One of which is stickiness, causing trouble to patients in application and having low spreading properties and rubbing requirement are also considered as disadvantages. Also stability of formulation for hydrophilic medication indicated some problems. Due to these drawbacks with the major group of semisolid preparations, the use of gelled formulation has expanded both in pharmaceutical preparations and in cosmetics. Gel is colloid containing 99 % part of liquid where macromolecular network of fibres built from a gelling substance and liquids are immobilized by surface tension between them. Despite of advantages a major problem is to delivery of hydrophobic natured drugs. Emulsion based approach can be used to incorporate lipophilic therapeutic moiety in gel based system to overcome this problem [4].

Methods of Formulation

Formulation of Nanoemulsion-gel can be summarized into following steps,

Screening of components

Preparation of Nanoemulsion

Preparation of Nanoemulgel.

Screening of components: Drug Solubility was determined in different oils by excess addition of drug into different components followed by continuously stirred 72 hours to achieve equilibrium. After that samples centrifuged and supernatant was taken and solubility was determined by appropriate analytical methods. Then, excipients in each category with the highest solubility of drug are selected for further studies.

Psedoternary phase diagram: Surfactant and cosurfactant (Nmix) were mixed in different ratios (2:1, 3:1 and 5:1). Each ratio chosen in increasing amount of surfactant respect to co-surfactant for a study on the phase diagrams. Here aqueous phase (Distilled water) used as dilution media. Oil and Nmix was mixed at different ratios from 9:1 to 1:9 in different vials for each Nmix. Main objective for this is to cover for the study to decide boundaries of phases formed in the diagrams. It wasdeveloped using titration method with help of water as aqueous media. Slow titration of oil and Nmix is performed and visual observations are made for transparency of Nanoemulsion. The state of Nanoemulsion is marked on one axis of aqueous phase, the second one of oil and the third one of Nmix (surfactant and co-surfactant) [5].

Preparation of Nanoemulsion: The drug is then solubilized in oil and oil is addend in to Nmix, this mixture is diluted with water to form of Nanoemulsion of given drug.

Preparation of Nanoemulgel: Gel base is prepared using 1g of the Carbopol in a required quantity of water. After complete swelling and dispersion of Carbopol solution during 24 hours period, prepared Nanoemulsion is slowly added under continues stirring. Addition of Triethanolamine gives homogeneous gel dispersion. Finally required remaining part is adjusted with distilled water Figure1.
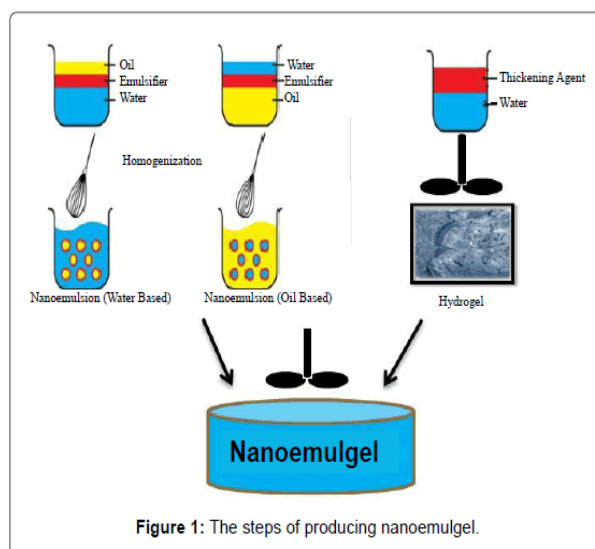

Figure 1: The steps of producing nanoemulgel.

Figure 1: The Steps of producing nanoemulgel

Components of Nanoemulsion

The main components of nanoemulsion are as follows: The selection of oil phase is the most important parameter in order to obtain a stabilized nanoemulsion, so that maximum amount of drug could solubilise in it. Usually, the oil which has maximum solubilising potential for selected drug candidate is selected as an oily phase for the formulation of nanoemulsions. This helps to achieve maximum drug loading in the nanoemulsions.

Mixture of oils can also be used to solubilised the maximum amount of drug. The different oils used for the nanoemulsion formulation are enlisted in Table 1.

Table 1: List of oils used in nanoemulsion.

Oils	Botanical Names
Arachis oil (Peanut oil)	Arachis hypogaea
Brahmi oil	Bacopa monnieri
Clove oil	Syzygiumaromaticum
Linseed oil (Flax seed oil)	Linumusitatissimum
Eucalyptus oil	Eucalyptus globules
Jojoba oil	Buxus chinensis
Peppermint oil	Mentha piperita
Neem oil	Azadirachta oil
Tea tree oil	Melaleuca alternifolia

Table 2: List of surfactants used in nanoemulsion.

Surfactants	Chemical Names
Kolliphor RH 40	Macrogolglycerolhydroxystearate
Ursolic acid	3β-Hydroxy-12-ursen-28-ic acid
Labrafil M 1944 CS	Oleoyl polyoxylglycerides
Lauroglycol FCC	Propylene glycol monolaurate
PEG MW>4000	Carbowax, polyglycol
PlurolOleique CC 497	Polyglyceryl-3 dioleate
Poloxamer 188	Poly(ethyleneglycol)-block-poly(propylene glycol)-block-poly(ethylene glycol)

Surfactants are the important component used for stabilizing the nanoemulsion system. The anionic, cationic, and nonionic types of surfactants are used in this system. Due to their different chemical nature, proper selection of surfactants (Table 2) becomes a crucial factor to obtain a stabilized delivery system. For the formation of a stable nanoemulsion, surfactants having proper HLB value are required. Cosurfactant plays an important role in reducing the polarity of surfactant to obtain a stabilized nanoemulsion. There are varieties of cosurfactants,

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which acts on surfactants interface, such as short- to medium-chain length alcohols (C3-C8). These are also helpful in increasing the penetrability of oil to get a stabilized formulation. The nature of aqueous phase mainly influenced the droplet size and the stability of nanoemulsion. The physiological milieu has diverse pH ranges varying from pH 1.2 (pH in stomach) to 7.4 and greater (pH of blood and intestine). In addition, the presence of various ions in the physiological milieu can also have considerable effect on the properties of nanoemulsions.

Evaluation of Nanoemulgel Formulations

The nanoemulgel formulations are characterized by the following techniques

Physicochemical parameters

The prepared nanoemulgel formulations are inspected visually for their color, homogeneity, consistency and phase separation.

pH Determination

The pH of the prepared formulations is determined by pH using meter. In this, the formulations are place in 250 ml beaker and immersing the pH meter into the formulation and record the readings. Same process is repeated for three times with same formulation.

Rheological investigation

The viscosity of the different nanoemulgel formulations is determined at 25°C using a cone and plate viscometer or Brookfield viscometer with appropriate spindle# and connected to a thermostatically controlled circulating water bath.

Globule size distribution in nanoemulgel

Globule size and distribution are determined by Malvern zetasizer. A 1 g sample is dissolved in purified water and agitated to get homogeneous dispersion. Sample is injected into photocell of zetasizer to obtain mean globule diameter and distribution.

Spreading Coefficient

Spreadability is determined by apparatus which consists of wooden block, which is provided by a pulley at one end. The spreadability is measured on the basis of 'Slip' and 'Drag' characteristics of nanoemulgels. A ground glass slide is fixed on this block. An excess of nanoemulgel (about 2 g) under study is placed on this ground slide. The nanoemulgel is then sandwiched between this slide and another glass slide. A 1 Kg weight is placed

on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the nanoemulgel between the slides. By putting weight of 80 g, the time (in seconds) required by the top slide to cover a distance of 7.5 cm with the help of string attached to the hook is noted [23].

A shorter interval indicates better spreadability, which is calculated by the formulae:

S=M.L/T

Where, S=Spreadability,

M=Weight tied to upper slide,

L=Length of glass slides and

T=Time taken to separate the slides completely from each other.

Extrudability Study (tube test)

This test is used to measure the force required to extrude the material from tube. The evaluation of extrudability is based upon the quantity of nanoemulgel extruded from lacquered aluminium collapsible tube on application of weight in grams required to extrude at least 0.5 cm ribbon of nanoemulgel in 10 seconds. The better extrudability is depend upon the quantity extruded [5]. The extrudability is than calculated by using the following formula

Extrudability=Applied weight to extrude nanoemulgel from tube (in g)/Area (in cm2).

Drug Content Determination

The drug content is determined by mixing appropriate amount of nanoemulgel formulation in suitable solvent. Then the solution is passed through whatman filter paper and filtrate is analyze for drug content by uv spectrophotometrically using the same standard plot by putting the value of absorbance as given by More.

Skin irritation test (patch test)

The preparation is applied on the properly shaven skin of rat and undesirable changes in colour, change in skin morphology should be checked up to 24 hours. If no irritation occurs the test is passed.

In vitro release study

The Franz diffusion cell (with effective diffusion area 3.14 cm2 and 15.5 ml cell volume) is used for the drug release studies. Nanoemulgel is applied onto the surface of dialysis membrane evenly and clamped between the

donor and the receptor chamber of diffusion cell. The receptor chamber is filled with freshly prepared phosphate buffer saline pH 5.5 solutions to solubilise the drug. The receptor chamber is stirred by magnetic stirrer. The samples (1.0 ml aliquots) are collected at suitable time interval. Samples are analyzed for drug content by UV visible after appropriate dilutions. The cumulative amount of drug released across the dialysis membrane is determined.

Drug release kinetic study

To analyze the mechanism of drug release from the topical nanoemulgel, the release data [27] are fitted to following equations:

Zero-order equation:

$Q=K_0t$

Where Q is the amount of drug released at time t, and K_0 is the zero-order release rate.

First-order equation:

$In (100-Q)=In 100 – K_1t$

Where Q is the percentage of drug release at time t, and K_1 is the first-order release rate constant.

Higuchi's equation:

$Q=K_2\sqrt{t}$

Where Q is the percentage of drug release at time t, and K_2 is the diffusion rate constant

Stability studies

The prepared nanoemulgels are packed in aluminium collapsible tubes (5 g) and subjected to stability studies at 5°C, 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH for a period of 3 months. Samples are withdrawn at 15-day time intervals and evaluated for physicalappearance, pH, rheological properties, drug content, and drug release profile. Accelerated stability studies of gellified nanoemulsion Stability studies are performed according to ICH guidelines. The formulations are stored in hot air oven at $37 \pm 2°$, $45 \pm 2°$ and $60 \pm 2°$ for a period of 3 months. The samples are analyzed for drug content every two weeks by UV-Visible spectrophotometer. Stability study is carried out by measuring the change in pH of formulation at regular interval of time.

CONCLUSION

Nanoemulgel based formulations may provide a better and reliable solution for delivery of hydrophobic drugs. A considerable lot of medications utilized as a part of treatment of skin disorders are hydrophobic natured and such medications can be conveyed successfully as Nanoemulgel where drug is incorporated into oil phase of Nanoemulsion and then merged with gel base. Incorporation of Nanoemulsion into gel matrix makes formulation dually control released system, Problems like creaming and phase separation which is associated with classical emulsion gets resolved with improved sparedability.

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